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Retroperitoneal Soft Tissue Sarcomas: A Pilot Study of Intraoperative Radiation Therapy

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This pilot study was conducted to evaluate the feasibility and tolerance of a multimodal therapy of retroperitoneal soft tissue sarcoma (STS), including intraoperative radiation therapy (IORT). Nineteen patients (14 primarily treated patients and 5 treated for a recurrent tumor) were included. Surgery included a complete resection (14), a partial resection (2), and no resection (2). The median IORT dose was 17 Gy. Thirteen patients also received an external radiation therapy (ERT). Nine patients received chemotherapy. There was no postoperative mortality. Immediate postoperative complications occurred in four patients (21%). Delayed complications occurred in six patients, including one lethal iliac artery disruption. With a median follow-up of 17 months, the 2-year disease-free survival rate was 60%, and the 2-year actuarial local control rate was 76%. A multimodality approach of treatment, including IORT and ERT and eventually chemotherapy, appears feasible in patients with retroperitoneal STS. However, the treatment-related morbidity appeared relatively high in this study.

KEY WORDS: **retroperitoneal tumors, soft tissue sarcoma, IORT, surgery**

INTRODUCTION

Soft tissue sarcoma (STS) is the generic denomination of a group of rare malignant tumors in which a retroperitoneal localization accounts for 10–15% [1,2]. Compared with sarcomas arising in other sites, retroperitoneal STSs are characterized by large size, frequent involvement of adjacent organs, and indistinct borders at time of surgery. Consequently, although a significant improvement in local treatment of STS may be recorded in the other sites, local control of retroperitoneal STS remains problematic, and local recurrence is the main cause of death for these diseases.

A complete tumor excision is the main condition for local control and long-term survival in patients with retroperitoneal STS [1,3]. However, due to the usually large tumor size, this is possible in only one-half of the patients and requires a visceral resection in as many as 79% of the cases [1,4]. Furthermore, in these sites, macroscopically complete resections are usually microscopically marginal because of the lack of anatomic boundaries, and local failure rates following such surgical treatment have been reported in 85–90% [1,2]. Thus even aggressive surgery remains insufficient in STS, and the association with other treatments would be needed. As in other sites, studies with external beam radiation therapy (ERT) have been conducted. Radiation doses ranging from 50 to 60 Gray (Gy) following complete retroperitoneal resection have been shown to reduce local recurrence [5,6]. However, considering the size of retroperitoneal STS, healthy and

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radiosensitive tissues or organs are usually included in the required volume and limit the dose of radiation to 45–50 Gy.

Intraoperative radiation therapy (IORT) is a recent modality of radiation therapy that allows a precise boost within a given target volume while sparing the adjacent healthy and critically radiosensitive tissues [7,8]. Some pilot studies and a small randomized trial have stressed the possible benefit of IORT in the treatment of retroperitoneal STS [9–12]. Therefore, a pilot study of multimodal therapeutical approach of retroperitoneal STS was done in our center, as part of a larger IORT evaluation program initiated in 1990. This multidisciplinary treatment consisted of surgery plus IORT and/or ERT pre- or postoperatively. The first results of this pilot study are reported.

PATIENTS AND METHODS

Patients

From January 1991 to June 1994, 51 patients, newly diagnosed (38) or recurrent (13) with retroperitoneal STS, were referred to our institution. Two patients refused treatment, two had metastases at presentation, 16 had already been operated on before referral without macroscopic tumor remnant at postoperative CT scan, and five were considered as not resectable. Twenty-six patients underwent surgery with conditions for a possible IORT, but peroperative radiotherapy was not delivered for seven patients after peroperative exploration because of peritoneal seeding (2 patients), negative frozen section (1 patient), intraoperative bleeding (1 patient), a duodenal suture in the planned IORT area (1 patient), a tumoral bed too large to be encompassed by the electron applicator (1 patient), and a technical problem on the linear accelerator (1 case). Finally, IORT was performed in 19 patients with retroperitoneal STS, including five with a locoregional tumor recurrence. There were 7 males and 12 females, with a median age of 61 years (range: 17–77 years). For 14 newly diagnosed sarcomas, the median tumor size was 13 cm (range: 4–37 cm). Two patients had metastatic disease: in one patient with bone multiple metastases, IORT was performed to improve the local control, and in one patient, three liver metastases were discovered and resected during surgery. In 12/14 patients, a first surgical procedure had already been performed before referral, consisting in biopsy for six patients, incomplete tumor removal for five, and a marginal resection in one. Among the five recurrent sarcomas included in this study, the median tumor size was 12 cm (range: 3–15 cm), and the median time from resection of initial tumor to recurrence was 26 months (range: 12–48 months). For those patients with recurrent disease, the initial treatment had been surgery alone (2 patients), surgery plus radiation therapy (2 patients), or surgery plus chemotherapy (1 patient). The main characteristics of patients and diseases are summarized in Table I.

TREATMENT METHODS

Treatment characteristics are given in Table II.

Surgery

Surgery was performed in a specially designed operating room located near the radiation room. Among 14 primary STS patients, a complete surgical resection could be achieved in 11, whereas gross tumor residue was left in three because of tumor infiltration of the internal iliac vessels, of the obturator area, and of the pelvic sidewall. Bloc resections of adjacent organs involved by the tumor were necessary in seven patients, consisting in a nephrectomy in six, a splenopancreatectomy in three, a left colectomy in one, a right colectomy in one, a rectal resection in one, and a hysterectomy in one. Moreover, in one patient, three liver metastases were discovered and resected. In the five patients presenting with recurrent STS, four complete resections could be achieved associated with a right colectomy for two and a nephrectomy for one. However, in one patient, infiltration of the vena cava resulted in an incomplete resection.

Intraoperative Radiation Therapy

Following surgery, an IORT was done on the tumor bed or on the tumor residues. Both the surgeon and the radiotherapist defined the size and the approximate depth of the target volume to determine the applicator diameter and to choose the electron energy according to dosimetric studies. A metallic electron applicator, either cylindric or elliptic, closed with a plexiglass-top specially designed and previously described [13], was positioned on the target zone in all cases but one. The median diameter of the applicator was 100 mm (range: 50–150 mm). Connection and docking to the head of the linear accelerator (Saturne 43 GE*) required a pantographic adaptor [8]. The median IORT dose was 17 Gy (range: 15–20 Gy) with a median level of electron energy of 12 MeV (range: 5–24 MeV). The median estimated depth of the 90% isodose was 26 mm (range: 10–38 mm). The median duration of the IORT procedure, defined as the time outside of the operating room, was 30 minutes (range: 20–40 mm). Details of the IORT procedure are given in Table III.

External Radiation Therapy

External beam radiation therapy was delivered to 13 patients, postoperatively in 12 patients. In 11/14 patients with primary STS, the median ERT dose delivered was 50 Gy (range: 40–60 Gy), with a 1.8–2 Gy per fraction, five fractions per week. One 77-year-old patient with a large 20 cm liposarcoma was irradiated preoperatively (50 Gy). Three primary STS were not given ERT because of: (1) no tumor residue at pathological examination in

TABLE I. Retroperitoneal Soft Tissue Sarcomas: Patients and Tumor Characteristics

No.	Sex	Age	Primary (P) recurrent (R)	Tumor size (mm)	Histology[a]	Grade	Comment
1	M	49	R	120	MHCF	II	
2	F	65	R	140	Liposarcoma	II	
3	F	71	P	40	Leiomyosarcoma	II	
4	F	51	R	30	Liposarcoma	III	
5	M	77	P	200	Liposarcoma	I	
6	M	41	P	230	MHCF	II	
7	F	67	P	150	Neurosarcoma	III	
8	M	69	P	50	Liposarcoma	n.s.	
9	M	67	R	120	Fibrosarcoma	III	
10	F	61	P	n.s.[b]	MHCF	II	
11	F	68	P	370	Liposarcoma	I	Simultaneous pancreatic and kidney cancers
12	M	17	P	120	ERM	n.s.	Multiple bone metastases
13	F	46	P	90	MHCF	III	
14	F	67	R	150	Liposarcoma	I	
15	F	45	P	150	Leiomyosarcoma	III	
16	M	71	P	100	Leiomyosarcoma	III	
17	F	61	P	n.s.	Liposarcoma	II	
18	F	43	P	180	Leiomyosarcoma	II	3 liver metastases
19	F	49	P	90	Liposarcoma	II	

[a]MHCF = malignant histiocytofibroma; ERM = embryonic rhabdomyosarcoma.
[b]n.s. = not specified.

TABLE II. Retroperitoneal Soft Tissue Sarcoma Patients Treated by Intraoperative Radiation Therapy: Treatment Characteristics

No.	Prior exploration	Surgical procedure[a]	Residual disease after surgery	IORT dose (Gy)	EBRT (Gy)	Chemotherapy[b] (no. of courses)
1	No	Reduction	Macroscopic	20	45 post-op	No
2	No	Resection (right hemicolectomy)	Microscopic	20	30 post-op	No
3	Reduction	Reduction	Macroscopic	15	40 post-op	pre-op A (2)
4	No	Resection	Microscopic	20	No	post-op B (6)
5	Biopsy	Resection	Microscopic	15	50 pre-op	No
6	Reduction	Reduction	Macroscopic	20	50 post-op	pre-op A (6)
7	No	Reduction (nephrectomy)	Macroscopic	20	50 post-op	post-op B (6)
8	Biopsy	Resection	No	17	No	No
9	No	Resection	Microscopic	20	No	No
10	Biopsy	Resection (nephrectomy)	Microscopic	17	50 post-op	No
11	No	Resection (right hemicolectomy + nephrectomy + SP)	Microscopic	17	No	No
12	Biopsy	No resection	Macroscopic	17	60 post-op	pre-op C (4)
13	Biopsy	Resection (hysterectomy + rectal resection)	No	18	No	pre-op A (4)
14	No	Resection (right hemicolectomy + nephrectomy)	Microscopic	17	No	No
15	Reduction	Resection (left colectomy + nephrectomy)	Microscopic	15	45 post-op	post-op B (6)
16	Resection	No resection	No	15	50 post-op	post-op B (1)
17	Reduction	Resection (left colectomy + nephrectomy + SP)	No	18	43 post-op	No
18	Biopsy	Resection (nephrectomy + SP + liver metastasectomies)	Microscopic	15	40 post-op	pre-op A (5)
19	Reduction	Resection	Microscopic	18	50 post-op	No

[a]SP = splenopancreatectomy.
[b]A = MAID combination (mesna/doxorubicin/ifosfamide/dacarbazine); B = CYVADIC combination (cyclophosphamide/vincristine/doxorubicin/dacarbazine); C = actinomycin D/vincristine/ifosfamide.

TABLE III. Retroperitoneal Soft Tissue Sarcomas: Intraoperative Radiation Therapy Characteristics

No.	Electron applicator diameter (mm)	Energy (MeV)	Dose (Gy)	Estimated depth (mm)	Time (minutes)
1	Elliptic flat (150 × 110)	n.s.[a]	20	n.s.	40
2	Elliptic beveled (150 × 110)	15	20	30	30
3	Circular beveled (80)	12	15	35	40
4	Circular beveled (60)	24	20	32	25
5	No applicator	75	15	20	30
6	Circular beveled (80)	24	20	n.s.	30
7	Circular beveled (80)	24	20	25	30
8	Elliptic beveled (130 × 90)	12	17	25	25
9	Circular flat (90)	5	20	10	35
10	Circular beveled (80)	24	17	38	20
11	Elliptic flat (130 × 90)	9	17	16	30
12	Circular beveled (50)	24	17	n.s.	25
13	Circular beveled (60)	21	18	28	40
14	Elliptic beveled (130 × 90)	18	17	n.s.	n.s.
15	Circular beveled (100)	12	15	25	20
16	Circular flat (100)	12	15	30	35
17	Elliptic beveled (150 × 110)	12	18	n.s.	35
18	Elliptic beveled (150 × 110)	18	15	34	30
19	Circular beveled (100)	9	18	15	30

[a]n.s. = not specified.

a patient who underwent a second surgical procedure following a first resection, (2) severe postoperative complication (complex pelvic fistula and ureteral necrosis), and (3) simultaneous cancers of the pancreas and of the kidney discovered during operation and surgically removed in addition to retroperitoneal liposarcoma. Among five patients treated for recurrent sarcomas, only two received ERT with a dose of 30 Gy and 45 Gy, respectively. For the other patients, ERT could not be delivered because of prior ERT (2 patients) or severe postoperative complication (1 patient).

Chemotherapy

Nine patients received chemotherapy. In five patients, this treatment was given preoperatively for a locally advanced tumor considered as not resectable. Four patients received a MAID regimen (mesna, doxorubicin, ifosfamide, dacarbazine) [14], and one patient with an embryonic sarcoma was treated with a combination of actinomycin D, vincristine, and ifosfamide. Four patients with grade 3 tumors were given a CYVADIC regimen (cyclophosphamide, vincristine, doxorubicin, dacarbazine) as adjuvant treatment [15].

Follow-Up

All patients were followed for immediate and secondary complications and for the development of local failure and distant metastases. Patients were seen 1 month after hospital discharge, and at 3-month intervals thereafter. At each follow-up, a medical history, a physical examination, a chest X-ray, and a pelvic and abdominal ultrasound examination were performed. A CT scan of the abdomen and the pelvis was obtained every 6 months. The mean and the median follow-up at evaluation were, respectively, 21 and 17 months (range: 4–37 months). The probabilities of local control and survival were calculated by the Kaplan-Meier product limit method [16]. Survival and local control durations were measured from the time of surgical procedure including IORT.

RESULTS

Mortality and Morbidity

No death occurred during the postoperative period. Postoperative complications occurred in four patients (21%) and consisted of: (1) a cerebral stroke occurring on the 6th postoperative day and resolving without sequellae, (2) a complex pelvic fistula occurring on the 8th postoperative day and consisting of a rectovaginal fistula with a bilateral ureteral necrosis, which required a colostomy, an internal ureteral stent, and a nephrostomy, (3) a case of anuria during the second postoperative week related to a left peri-ureteral hematoma in a patient who had a contralateral nephrectomy, which was resolved with an internal derivation by an ureteral stent, and (4) an external pancreatic fistula, 15 days after a splenopancreatectomy, which resolved under medical treatment. The last three postoperative complications occurred outside the IORT field and were not considered as IORT-related.

Six late complications were observed in five patients and resulted in death for one patient (5%). This fatality was due to bleeding related to an external iliac artery disruption, 4 months after surgery for a primary liposarcoma with an expansion toward the iliofemoral area. This

patient was 77 years old and received 50 Gy in 5 weeks preoperatively. Surgery consisted of marginal resection of the tumor with a difficult artery dissection. The IORT procedure consisted of a 15 Gy dose directed to the iliac muscle and the base of the femoral triangle, with a field of 15 × 20 cm, too large to allow the placement of the electron applicator.

The other late complications were: (1) one dehydration with electrolyte disorders, 2 months after surgery, (2) one moderate lymphoedema of the lower limb, which developed 11 months after the treatment, (3) one moderate lumbar plexopathy occurring 6 months after the surgical resection of a leiomyosarcoma with 15 Gy IORT and 45 Gy postoperatively, which resolved after 4 months, and (4) two cases of chronic enteritis, without any sign of recurrence on a complete checkup, were observed 8 and 10 months after the treatment.

Locoregional Failures

Four local or regional recurrences occurred and affected 2/14 patients treated for their first tumor event and 2/5 patients treated for a recurrence.

One local failure was observed in the IORT field 13 months after a marginal resection of a liposarcoma recurrence, 20 Gy IORT, and adjuvant chemotherapy. This patient died 10 months later.

One local recurrence occurred outside the IORT field but inside the ERT field 19 months after IORT for a recurrent liposarcoma. This was surgically removed. Nine months later, a peritoneal sarcoma diffusion was diagnosed and treated by palliative chemotherapy. This patient is alive with cancer 9 months later.

One patient with a malignant fibrous histiocytoma of the right retroperitoneum experienced a local recurrence in the left pelvis and outside the ERT field at 13 months. A new resection with left colectomy was performed. No recurrent disease was found on the initial tumor bed at laparotomy. Then 50 Gy were delivered to the recurrent tumor bed. The patient is alive and disease-free 16 months later.

One patient had a regional recurrence in the pelvis occurring 15 months after resection with IORT of a large median liposarcoma. In this patient, no ERT was done because of the peroperative discovery and treatment of a pancreatic cancer and a renal cell carcinoma. The patient was disease-free 2 months after the resection of this recurrence.

In summary, for the entire series, actuarial local control rates are 100% at 1 year and 76% at 2 years.

Metastatic Failures

A distant failure was observed as first site of recurrence in three patients. All were treated for a recurrent STS. Metastases were peritoneal (1 patient), pulmonary and soft tissue sites (1 patient), and pleural (1 patient), occurring 8, 7, and 8 months, respectively, after surgery. One patient, treated for a primary alveolar rhabdomyosarcoma with initial bone metastatases, died of progressive disease 11 months after surgery.

Survival and Disease Status

Evolution and disease status are shown in Table IV. For the entire series, the overall actuarial survival rate was 80% at 1 year and 60% at 2 years. The actuarial disease-free survival rate was 68% at 1 year and 32% at 2 years.

At the time of analysis, 12/19 patients were alive and disease-free 6–31 months following the IORT procedure, two patients were alive with evidence of cancer at 15+ and 37+ months, four patients had died from cancer at 11 to 23 months, and one patient had died at 4 months from a treatment complication.

Among the patients treated for their first tumor, 12/14 patients were alive and disease-free, two of them after salvage surgery for a limited regional recurrence. Two patients had died of cancer (1 patient), or of a treatment complication (1 patient). Three of the five patients treated for recurrent STS had died from STS, and two patients were alive with disease.

DISCUSSION

The treatment of retroperitoneal STS remains a continuous challenge. The first factor affecting the course of retroperitoneal STS remains the ability to perform a complete surgical resection. Several series have reported 5-year survival rates from 29–53% [1–3,5,17,18]. The 5-year survival rate after complete resection is 54–64% as compared to one of 17 to 33% following partial resection [1,3]. Even after a complete resection, local failures remain frequent. A compiled analysis of 310 patients treated with a complete resection found recurrence and local recurrence rates of 63% and 47%, respectively [19]. In an attempt to improve the local control rate, postoperative ERT was first proposed. Some series have not shown any benefit with postoperative irradiation [1,3]. However, Cody et al. [5] reported a 5-year survival rate of 53% in a pilot study of 15 patients with retroperitoneal STS treated with a combination of surgery and irradiation. This was better than the results of 23 patients treated in the same institution at the same period with complete surgical resection alone, with a 5-year survival rate of 33% [5]. Tepper et al. [6] also reported encouraging results for 17 patients following surgery and postoperative ERT with a 54% 5-year survival rate and a 54% local control rate. In this report, 67% of the patients had local failure when the delivered dose of radiation was lower than 50 Gy as compared with 17% of the patients treated with doses of 60 Gy or more [6]. Fein et al. [19] reported a 5-year local control rate of 72% in 21 retroperitoneal STS patients: 2/8 patients treated with a total dose of

TABLE IV. Evolution and Disease Status of Patients With Retroperitoneal Soft Tissue Sarcomas Treated by IORT*

No.	Date of surgery + IORT	Morbidity	Recurrence	Disease status[a]	(follow-up)
1	01.91	No	8 months: peritoneal sarcomatosis	DFC	15 months
2	11.91	Ionic disturbances	19 months: local failure (resection)	AWC	37 months
3	02.92	Sequellar lymphoedema	No	ADF	31 months
4	06.92	No	13 months: local failure in the IORT field	DFC	23 months
5	06.92	Iliac artery disruption	No	DTC	4 months
6	08.92	No	13 months: regional failure (resection + ERT[b])	ADF	29 months
7	09.92	No	No	ADF	27 months
8	01.93	No	No	ADF	24 months
9	01.93	Cerebral stroke	7 months: distant failure (pulmonary + soft tissues)	DFC	12 months
10	03.93	No	No	ADF	21 months
11	04.93	No	15 months: regional failure (resection)	ADF	17 months
12	07.93	No	Distant bone progression	DFC	11 months
13	07.93	Pelvic fistula	No	ADF	16 months
14	09.93	Anuria	8 months: distant failure (pleural)	AWC	15 months
15	02.94	Neuropathy + chronic enteritis	No	ADF	11 months
16	02.94	No	No	ADF	7 months
17	04.94	Chronic enteritis	No	ADF	9 months
18	06.94	Pancreatic fistula	No	ADF	6 months
19	06.94	No	No	ADF	6 months

*IORT = intraoperative radiation therapy.
[a]DFC = dead from cancer; AWC = alive with evidence of cancer; ADF = alive and disease-free; DTC = dead from treatment complication.
[b]External radiation therapy.

radiation higher than 55.2 Gy locally failed vs. 5/13 patients with a dose lower than 55.2 Gy. However, because of the usually large volume of retroperitoneal STS, doses of 50 Gy or more are frequently not possible owing to the radiosensitive organs included in the irradiated volume, such as the bowel, liver, and kidneys. However, IORT has the theoretical advantage of allowing a radiation boost on a limited volume, with a direct visualization of the target—the tumor residue or the tumor bed—while sparing critical surrounding organs.

Tolerance to IORT has been evaluated. Experimental animal and pilot studies have specified the tolerance of many organs: a single dose of radiation within the 15–20 Gy range is well tolerated [20–22]. However, several animal studies have pointed out the nerve sensitivity to an IORT dose. The higher the dose, the higher the frequency and earliness of neuropathies, with a dose threshold of 20 Gy [23,24]. Nerve roots such as the lumbosacral plexus may be more sensitive than nerve trunks like the sciatic nerve [25]. Published results of IORT given for various cancers, including gastric, pancreatic, and rectal cancers, have confirmed tolerance to the IORT procedure [7,26,27]. No limiting biological or immunological changes have been observed following IORT [28]. For retroperitoneal STS, only a few series are available. One severe neuropathy and one small bowel obstruction requiring a surgical exploration were observed in two out of 20 patients treated at the Mayo Clinic [10]. Willett et al. [9] observed two cases of sensory neuropathies in 12 retroperitoneal STS treated at Massachusetts General Hospital. In the National Cancer Institute randomized trial comparing the association of IORT 20 Gy with low dose postoperative ERT 35–40 Gy and high dose postoperative irradiation (50–55 Gy), the reported incidences of acute (7%) and chronic enteritis (20%) were significantly lower in the IORT-treated patients than in the patients treated with high dose ERT, i.e., 60% and 50%, respectively. The main limiting side effect of IORT was neurotoxicity; neuropathies occurred in 9/15 patients treated with IORT as compared with 1/20 patients treated without IORT [11,12]. In the present series, only one regressive neuropathy was observed.

Nerve tolerance may be related to certain parameters such as dose of IORT, depth of the treated volume, and dose of the associated external beam RT. The association of an aggressive surgery to ensure complete gross tumor resection and a high dose of radiotherapy may lead to severe vascular damage. In our study, a fatal arterial disruption was observed. In this case, the complication also may have been favored by a patient age of 77 years, underlying atherosclerosis, and finally an unusual IORT modality, which was performed without electron applicator. Such a complication has previously been reported. Tepper et al. [21] described a case of bleeding from the iliac artery occurring 8 months after IORT. Garton et al. [29] reported a rupture of an iliac artery in the ileum for a Mayo patient treated with IORT for a gynecologic cancer. A rupture of the common femoral artery was reported by Dubois et al. [30] the day after surgical resection of a sarcoma with IORT. Moreover, Wilkowski et al. [31] pointed out the risks of arterial complications in the case of underlying atherosclerosis.

As concerns the efficacy of IORT in retroperitoneal STS treatment, some pilot studies have reported encouraging results. Willett et al. [9] reported a multimodal treatment for 12 retroperitoneal STS associating pre-operative ERT, maximal tumor removal, and 10–20 Gy IORT; two patients with incomplete tumor resection recurred; among 10 patients given IORT after a gross complete resection, only one local recurrence was noted associated with a peritoneal diffusion, and seven patients remained disease-free. The 4-year disease-free survival was 64% [9]. In the Mayo Clinic series, 20 patients were treated with the combination of preoperative ERT 45–60 Gy, maximal surgical resection, and IORT 10–20 Gy. The locoregional failure rate was 25% with only one recurrence (5%) in the field of IORT, three recurrences occurring in the retroperitoneum outside the IORT field and one peritoneal failure [10]. In the NCI study, with a median follow-up of 8 years, similar overall survival was observed in the two treatment groups. However, local failures occurred in 16/20 control patients as compared with 6/15 IORT-treated patients, the difference being statistically significant ($P = 0.05$) [11,12]. In the present study, the low number of patients included and the short follow-up do not make it possible to draw any conclusion about the efficacy of IORT. However, the fact that only 4/19 patients and only 2/14 patients treated for the first time had locally recurred at the time of the evaluation appears promising.

The possible benefit of a chemotherapy on survival rates, by both a reduction of the metastatic rate and a reduction in the local failure rate, remains controversial [32]. However, a statistically significant decrease in the local recurrence rates has been observed in four randomized studies of adjuvant chemotherapy in STS, mainly sarcomas of the extremities [33–36]. In addition, a significant decrease in the metastatic failure rates was reported in two trials [36,37]. Yet for retroperitoneal STS, no benefit with adjuvant chemotherapy has been reported so far [32]. Moreover, an optimal delivery of the chemotherapy and the possible effect of this treatment on the incidence and severity of side effects of surgery and radiotherapy will be of future interest.

CONCLUSIONS

This pilot study confirms the feasibility of an intraoperative radiation boost. The precise definition of doses and irradiated volumes and accuracy of the IORT technique are necessary to reduce the procedure-related side effects, particularly when nerves cannot be excluded from the IORT field. Preliminary results like those observed in this series are encouraging, particularly in patients with retroperitoneal STS treated for the first time. However, further preferably randomized studies should be planned in order to confirm the benefit of IORT and to determine the most appropriate combinations of treatment.

REFERENCES

1. Storm FK, Mahvi DM: Diagnosis and management of retroperitoneal soft tissue sarcomas. Ann Surg 214:2–10, 1991.
2. Alvarenga JC, Ball AB, Fisher C, Fryatt I, et al.: Limitations of surgery in the treatment of retroperitoneal sarcomas. Br J Surg 78:912–916, 1991.
3. Karakousis CP, Velez AF, Emrich LJ: Management of retroperitoneal sarcomas and patient survival. Am J Surg 150:376–380, 1985.
4. Jacques DP, Coit DG, Brennan MF: Soft tissue sarcoma of the retroperitoneum. In Shiu MH, Brennan MF (eds): "Surgical Management of Soft Tissue Sarcoma." Philadelphia: Lea & Febiger, 1989, p 157–169.
5. Cody HS, Turnbull AD, Fortner JG, Hajdu SI: The continuing challenge of retroperitoneal sarcomas. Cancer 47:2147–2152, 1981.
6. Tepper JE, Suit HD, Wood WC, Proppe KH, et al.: Radiation therapy of retroperitoneal soft tissue sarcomas. Int J Radiat Oncol Biol Phys 10:825–830, 1984.
7. Abe M, Takahashi M: Intraoperative radiotherapy: The Japanese experience. Int J Radiat Oncol Biol Phys 7:863–868, 1981.
8. Romestaing P, Gilly FN, Sentenac I, Rocher F, et al.: Radiothérapie intra-opératoire. Technique, résultats préliminaires, indications. Lyon Chir 82:121–128, 1989.
9. Willet CG, Suit HD, Tepper JE, Mankin HJ, et al.: Intraoperative electron beam radiation therapy for retroperitoneal soft tissue sarcoma. Cancer 68:278–283, 1991.
10. Gunderson LL, Nagorney DM, Mac Ilrath DC, Fieck JM, et al.: External beam and intra-operative electron irradiation for locally advanced soft tissue sarcomas. Int J Radiat Oncol Biol Phys 25:647–656, 1993.
11. Kinsella TJ, Sindelar WF, Lack E, Glatstein E, et al.: Preliminary results of a randomized study of adjuvant radiation therapy in resectable adult retroperitoneal soft tissue sarcomas. J Clin Oncol 6:18–25, 1988.
12. Sindelar WF, Kinsella TJ, Chen PW, De Laney TF, et al.: Intraoperative Radiotherapy in retroperitoneal sarcomas: Final results of a prospective, randomized, clinical trial. Arch Surg 128:402–410, 1993.
13. Richaud P, Bussières E, Landriau S: Réalisation d'un "sabot" adaptable sur les localisateurs utilisés lors d'une irradiation peropératoire. Bull Cancer Radiother 78:187–189, 1991.
14. Elias AD, Ryan L, Aisner J, et al.: Response to mesna, adriamycin, ifosfamide and decarbazine in 105 patients with metastatic or unresectable sarcomas and no prior chemotherapy. J Clin Oncol 7:1208–1216, 1989.
15. Benjamin RS, Gottleib JA, Baker LH, et al.: CYVADIC vs CYVADACT: A randomized trial of cyclophosphamide, vincristine and adriamycin, plus either decarbazine or actinomycin D in metastatic sarcomas. Proc Am Assoc Cancer Res 17:256, 1976 (abstract).
16. Kaplan EL, Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
17. Bevilacqua RG, Rogatko A, Hajdu SI, Brennan MF: Prognostic factors in primary retroperitoneal soft tissue sarcomas. Arch Surg 126:328–334, 1991.
18. MacGrath PC, Neifeld JP, Lawrence WJ, DeMay RM, et al.: Improved survival following complete excision of retroperitoneal sarcomas. Ann Surg 200:200–204, 1984.
19. Fein DA, Corn BW, Lanciano RM, Herbert SH, et al.: Management of retroperitoneal sarcomas: Does dose escalation impact on locoregional control? Int J Radiat Oncol Biol Phys 31:129–134, 1995.
20. Sindelar WF, Kinsella T, Tepper JE, Travis EL, et al.: Experimental and clinical studies with intra-operative radiotherapy. Surg Gynecol Obstet 157:205–219, 1983.
21. Tepper JE, Gunderson LL, Orlow E, Cohen AM, et al.: Complications of intraoperative radiation therapy. Int J Radiat Oncol Biol 10:1831–1839, 1984.
22. Noyes RD, Weiss SM, Krall JM, Sause WT, et al.: Surgical complications of intraoperative radiation therapy: The Radiation Therapy Oncology Group experience. J Surg Oncol 50:209–215, 1992.
23. LeCouteur RA, Gillette EL, Powers BE, Child G, et al.: Peripheral neuropathies following experimental intra-operative radiation therapy (IORT). Int J Radiat Oncol Biol Phys 17:583–590, 1989.

24. Kinsella TJ, DeLuca AM, Barnes M, Anderson W, et al.: Threshold dose for peripheral neuropathy following intra-operative radiotherapy (IORT) in a large animal model. Int J Radiat Oncol Biol Phys 20:697–701, 1991.
25. Vujaskovic Z, Gillette SM, Powers BE, LaRue SM, et al.: Intraoperative radiation (IORT) injury to sciatic nerve in a large animal model. Radiother Oncol 30:133–139, 1994.
26. Gilly FN, Braillon G, Gérard JP, Dubois JB, et al.: IORT in pancreatic carcinoma: Report of the French experience on 126 patients. Hepato-Gastroenterol 20:A69, 1994.
27. Bussières E, Richaud P, Gérard JP, Bérard P, et al.: Intra-operative radiation therapy (IORT) in rectal cancers: Report of the French IORT group about 112 patients. Hepato-Gastroenterol 20:A74, 1994.
28. Bussières E, Richaud P, Gualde N: Intra-operative electron beam radiotherapy and abdomino-pelvic surgery for cancer: Influence on immunological parameters. Eur J Surg Oncol 18:425–432, 1992.
29. Garton GR, Gunderson LL, Webb MJ, Wilson TO, et al.: Intraoperative radiation therapy in gynecologic cancers: The Mayo Clinic experience. Gynecol Oncol 48:328–332, 1993.
30. Dubois JB, Debrigode C, Hay M, Gely S, et al.: Intra-operative radiotherapy in soft tissue sarcomas. Radiother Oncol 34:160–163, 1995.
31. Wilkowski R, Kiszel Z, Rube C, Busch M, et al.: Modifications morphopathologiques des vaisseaux sanguins après RPO et radiothérapie externe des cancers pancréatiques non résécables. Lyon Chir 90:227–228, 1994.
32. Glenn J, Sindelar WF, Kinsella TJ, Glatstein E, et al.: Results of multimodality therapy of resectable soft-tissue sarcomas of the retroperitoneum. Surgery 97:316–324, 1985.
33. Benjamin RS, Terjanian TO, Fenoglio CJ, Barkely HT, et al.: The importance of combination chemotherapy for adjuvant treatment of high-risk patients with soft-tissue sarcomas of the extremities. In Salmon SE (ed). "Adjuvant therapy of cancer V." Orlando: Grune & Stratton, 1987, p 735–744.
34. Bramwell V, Rouëssé J, Steward W, Santoro SA, et al.: Adjuvant CYVADIC chemotherapy for adult soft tissue sarcoma: Reduced local recurrence but no improvement in survival: A study of the European Organization for Research and Treatment of Cancer soft tissue and bone sarcoma group. J Clin Oncol 12:1137–1149, 1994.
35. Chang AE, Kinsella TJ, Glatstein E, Baker A, et al.: Adjuvant chemotherapy for patients with high-grade soft-tissue sarcomas of the extremity. J Clin Oncol 6:1491–1500, 1988.
36. Ravaud A, Bui NB, Coindre JM, Kantor G, et al.: Adjuvant chemotherapy with Cyvadic in high-risk soft tissue sarcoma: A randomized prospective trial. In Salmon SE (ed). "Adjuvant Therapy of Cancer VI." Philadelphia: WB Saunders 1990, p 556–566.
37. Gherlinzoni F, Picci P, Bacci G, de Cristofaro R, et al.: Late results of a randomized trial for the treatment of soft tissue sarcomas (STS) of the extremities in adult patients. Proc Am Soc Clin Oncol 12: abst 1633, 1993.